CHAPTER 6

Smallpox: A Primer

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Smallpox, is a virus that plagued humanity for millennia. It was the first and only disease ever intentionally eradicated from the face of this planet, a scourge defeated in a remarkable, never-before-attempted campaign of generosity and cooperation by the nations of the world. Its eradication was a triumphant symbol of science and dogged persistence winning over nature. Moreover, its eradication was a gift of man to all mankind.

Yet, is it possible that the same hand of man, that once rid the scourge of smallpox from the world, will be used to unleash this terror again on its unprotected citizens? This chapter, by providing a thorough review of the history, epidemiology, and current risks associated with this dreaded disease, addresses that question and its implications for the American public.

Origins of Smallpox

Smallpox has been described as one of the great scourges of mankind.[1] Every corner of the world has felt its grip and known its devastation. Historians speculate that smallpox first appeared around 10,000 B.C. in the agricultural settlements in northeastern Africa. From there, it probably spread to India via Egyptian merchants. There is evidence smallpox is at least 3,000 years old. It was known in China as early as 1122 B.C. Its scars have been found on the mummy of Pharaoh Ramses V, who died in 1157 B.C., as well as on other mummies from the 18th and 20th Egyptian dynasties.[2,3]

The first known smallpox epidemic was recorded in 1350 B.C. During the Egyptian-Hittite war that year, Egyptian prisoners unwittingly spread smallpox to the Hittites. Even the Hittite King Suppiluliumus I and his heir fell victim to the virus. It devastated their civilization and assured the Egyptians victory.[4]

Records also show the ancients recognized subsequent immunity in those who survived the disease. Thucydidus noted this curiosity during the Athenian epidemic in 430 B.C. Rhazes, considered the greatest physician of Islam and the Medieval Ages, likewise documented post-infection immunity in 910 A.D., when he recorded the first known medical description of smallpox and its transmission.[5]

Insidiously, smallpox made its way around the world leaving devastation in its wake. The Crusades, the expansion of the Arab world, and the colonization of the Americas—wherever an infected individual came in contact with peoples previously unexposed—contributed to the spread of smallpox. Smallpox reached Europe in the 5th century and was a leading cause of death in the 16th and 17th centuries. It affected everyone, regardless of age, sex, or socioeconomic status. The commoners of Europe were hit particularly hard. An estimated 400,000 died from smallpox every year during the 18th century. One third of the survivors were scarred and many were blinded.[6]

In the 1500s, the Spanish and Portuguese transported the disease to the New World, which decimated the Aztec and Inca populations in Mexico and South America. Likewise in North America, European colonizers carried the smallpox virus that devastated the native populations there. Sadly, the first documented use of smallpox as a weapon can be attributed to the British, who gave blankets contaminated with smallpox to troublesome Native American Indians in Quebec in the late 18th century to intentionally expose them to the virus.[7]

Not only common folk succumbed to smallpox. The famous and powerful who died from smallpox includes: Marcus Aurelius in A.D. 180; King Boranarja IV of Siam in 1534; William II of Orange in 1650; Emperor Gokomyo of Japan in 1654; Queen Mary II of England in 1694; King Nagassi of Ethiopia in 1700; Tsar Peter II of Russia in 1730; and, King Louis XV of France in 1774. It is said that President Lincoln was feverish with smallpox when he gave the Gettysburg address in 1863. Two days afterwards he broke out with the trademark rash.[8, 9]

Epidemiology

Smallpox is a viral disease unique to humans. Highly contagious, it predominately spreads person–to-person via inhalation of sub-micron of water droplets (to which viral particles attach) exhaled by infected individuals. However, as with common-cold viruses, the smallpox virus can be introduced to the human body by touching a contaminated object, then subsequently touching one's nose or mouth with the contaminated hand. The virus is not known to enter a body directly through the skin. There is no known animal or insect reservoir or vector.

There are two principal forms of the virus—*variola major* and, a milder form, *variola minor*. *Variola major* historically "resulted in case fatality rates of 30 percent or higher among the unvaccinated [3 percent in the vaccinated], whereas *variola minor* case-fatality rates were customarily 1 percent or less."[10]

People with smallpox were most infectious from the onset of their papular rash through the first 7 to 10 days of the rash. Approximately 30 percent of susceptible contacts came down with the disease. As scabs formed, respiratory infectivity waned, but patients were considered infectious until all scabs separated.[11]

The first symptoms of natural infection occurred usually 10 to 14 days after exposure with severe aching, malaise, prostration, headache, backache, and fever. Two to three days later, a macropapular rash appeared on the mucosa of the mouth and pharynx, face, and forearms. The rash then spread to the trunk and legs. Lesions quickly progressed to pustular vesicles. Fever remained throughout the course of the disease and pain was common as the pustules evolved. About 8 to 14 days after onset, scabs formed and later separated, leaving a pitted complexion. Death usually occurred during the second week. The only way to prevent the spread of smallpox was patient isolation and vaccination.[12, 13, 14]

Variolation as Inoculation

Survivors of smallpox—the "speckled monster" in the 18th century vernacular—were known to have immunity. For this reason, doctors and

others intentionally exposed healthy people to the disease in hopes that they too would become immune. They collected samples from vesicles, pus from pustules, or scabs and introduced them into the nose or skin of healthy humans. This method of inoculation, or "variolation" as it was first called, is believed by some to have originated in China.[15] Mountain hermits there are known to have used smallpox inoculation as early as the 10th century AD.[16] It became widely popular in China during the period 1567 to 1572. "In fact, it seems that the operation [of variolation] had been practiced quite discreetly in numerous African countries, in India, in China, and even in Europe for a long time."[17] It was during the 17th century that the practice of variolation spread to the Ottoman Empire, where it became common practice.

Lady Mary Wortley Montague, the wife of a British Ambassador to the Sublime Porte in the Ottoman Empire, introduced variolation to England.[18] She was a survivor of smallpox, which had disfigured her beautiful face. Because of her personal experience with the disease, the Turkish preventive practice of "engrafting" fascinated her. This procedure entailed making four or five scratches or a puncture in the arm and introducing material from smallpox pustules. To prevent her 5-year-old son from getting smallpox, she had him variolated in 1718. After returning to England in 1721, she had her 4-year-old daughter immunized in the presence of the King's court doctor. News of the inoculation spread. The procedure was tested in 1721 on six prisoners sentenced to death and six orphaned children and, in 1722, two daughters of the Princess of Wales were variolated. All developed immunity to the virus.[19]

Variolation was the only known way to prevent the spread of smallpox. However, intentionally introducing smallpox virus into the skin could be harmful, if not deadly. Over time, practitioners used a variety of practices to prepare their patients, such as taking of blood, enemas, and strict diet with purging. Edward Jenner, the British physician who developed the first smallpox vaccination, described his preparation for variolation when he was eight years old: "there was taking of blood until the blood was thin; purging until the body was wasted to a skeleton; and starving on a vegetable diet to keep it so."[20] This preparation took 2 to 4 weeks, followed by 10 to 15 days of actual sickness from side effects. The effects were severe enough to keep the patient in bed and convalescence

took up to one month.[21] Complicating the process was that inoculation could be fatal. About 2 people died for every 100 variolated.[22]

Even with the high risks, variolation spread throughout Europe. While not everyone could afford to receive the inoculation, nobility in Austria, Prussia, France, and Russia were variolated. The procedure soon reached the New World. In 1721, it was used to stop an epidemic in Boston. Now variolation quickly spread throughout the colonies. In 1776, the colonial soldiers under George Washington failed to take Quebec from England because a smallpox epidemic had cut their size in half; the British were saved because they had received inoculation. By 1777, Washington ordered all his soldiers variolated. To prevent another epidemic, he also had all new recruits immunized as soon as they entered duty.[23, 24]

Era of Vaccination

Back in England, milkmaids became the unlikely subjects of rudimentary medical research. It had been observed that milkmaids tended to escape outbreaks of smallpox unaffected. Edward Jenner suspected a connection between the pox marks (caused by cowpox) on the milkmaids' hands and their immunity to smallpox. In 1796, Jenner inoculated an 8-year-old boy, John Phipps, with the cowpox virus. Six weeks later, he vaccinated the same boy with smallpox. The boy did not get sick. He repeated the procedure months later with the same results. The boy was immune. Jenner had discovered a crude smallpox vaccine.[25]

Jenner tried to publish his discovery through the Philosophical Transactions of the Royal Society but the Society rejected his "incredible" ideas. Finally, he resorted to publishing his findings himself, titled "An inquiry into the causes and effects of the *variolae* vaccine, a disease discovered in some of the western counties of England, particularly Gloucestershire, and known by the name of the cow pox."[26] While not initially accepted, vaccination with cowpox pustule fluid was eventually tested and confirmed. The era of smallpox vaccination had arrived.[27]

By 1800, vaccination had permeated most of Europe and America, with about 100,000 people vaccinated worldwide. Over the next 150 years, healthcare providers all over the world gradually adopted

vaccination. Nevertheless, the disease persisted where people went unvaccinated. As late as the 1930s, smallpox infected up to 50,000 people a year in the United States. An epidemic even broke out in 1947 in New York City when a businessman traveling from Mexico brought smallpox into the city. Within a couple of weeks, 13 people died. Massive hysteria occurred and the city vaccinated six million residents. The last case in the United States occurred 1949 in Hidalgo County, Texas. Nevertheless, the rest of the world continued to experience smallpox well up into the 1970s. [28, 29, 30]

Eradication

In 1953, the newly created World Health Organization (WHO) suggested that smallpox be eradicated from the human race. They tried again in 1958. Little progress occurred until 1967 when the Union of Soviet Socialist Republics and the United States gave $2.5 million to fund the initiative. D.A. Henderson of the Centers for Disease Control and Prevention headed the campaign. Its goal was to interrupt, permanently, the chain of transmission of smallpox.[31]

When the eradication campaign began, smallpox was endemic to five regions of the world—South America, West and East Africa, India, and Indonesia. The plan was to go to each region and vaccinate the entire population there; but the effort quickly ran short of vaccine. A more economical approach was called for. Surveillance and containment became the new plan of attack. It focused on currently infected households. The process involved finding a case of smallpox, isolating the patient, and vaccinating all the people in contact with or within a short distance, or ring, of the patient. Then medical workers extended the ring of vaccination to a practical distance. They called the process surveillance and containment, or ring vaccination.

The search was enormous. Every single case of smallpox had to be hunted down by a determined medical professional or volunteer. Nevertheless, the strategy worked with dramatic results. By 1971, Latin America was free of smallpox. Indonesia and South Africa followed closely behind. India, next on the list, was a huge success story. In 1973,

WHO volunteers traveled to every village in the country. More than 120,000 healthcare workers visited over 100 million homes. Eighteen months later, smallpox was gone. [32, 33]

The last two remaining strongholds for smallpox were Bangladesh and East Africa. In 1975, the battle in Bangladesh was won.[34] Through 1977, smallpox persisted in the region of Ethiopia, Kenya, and Somalia. The last case in Ethiopia was diagnosed in August 1976; the last in Kenya was February 1977. As for Somalia, the WHO staff and epidemiologists rooted out the last known case of smallpox on 26 October 1977. With the victim in isolation, the chain of transmission was finally broken. [35]

The WHO needed two years with no further reports of smallpox to declare success. Three cases of smallpox did develop in 1978 at the Medical School at the University of Birmingham in England, due to careless handling of the virus stored in its laboratory. However, by the fall of 1979, it was clear that no further natural cases of smallpox were to be found. On 8 May 1980, WHO declared smallpox eradicated.[36]

The Virus Lives On

Smallpox may have been eradicated, but its etiological agent, the *variola* virus itself, continued to exist in many laboratories around the world. The incident in Birmingham in 1978 and the high transmissibility potential of the virus flagged the need for stricter controls. The WHO recommended that all laboratories storing the virus destroy their stocks or transfer them to two WHO-sanctioned, high-security laboratories. These laboratories are currently the Russian State Center for Research on Virology and Biotechnology in Koltsovo, Novosibirsk (Siberia) and the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. [37, 38] These are the only two locations in the world where the virus is known to still exist.

Variola has been on death row for years. Three times, the Assembly of WHO recommended dates by which all stocks of the virus should be destroyed—31 December 1993, 30 June 1995, and 30 June 1999. Each time, as the dates for destruction drew near, scientists, medical providers, and world leaders began to question the prudence of destroying the last of the *variola* virus. Those in favor of destruction argue the risk of a virus

release outweighs the research benefits the live virus provides. They contend the smallpox virus must be destroyed so it can never again threaten mankind. Those who favor maintaining the virus believe the stocks are a counterbalance to terrorism and a source of future research. Most recently, on 22 May 1999, the Assembly of the WHO granted *variola* its latest stay of execution, until 2002, to determine if the live virus is still required for research.[39, 40]

Vaccination and Diminished Protection Over Time

Vaccination with *vaccinia* was the modern way to protect against smallpox. With its eradication in 1980, the WHO recommended all countries cease vaccinating their citizens.

In the U.S., healthcare officials had already stopped vaccination. Because of the implementation of worldwide vaccination and quarantine programs, "the risk of importation of smallpox into the United States was reduced by the 1960s. Consequently, United States discontinued routine, public smallpox vaccination in 1972."[41] Additionally, the vaccination of healthcare professionals and international travelers was discontinued in 1982. That same year, the only active, licensed producer of the vaccine ended production for general use. Finally, in July 1988, the military stopped routine smallpox vaccinations. Consequently, since 1972, very few American citizens have been immunized with *vaccinia*. This makes our population potentially susceptible to smallpox.[42, 43]

Studies show that receiving one dose of the vaccine provides more than 95 percent of the recipients an antibody titer level of at least 1:10, furnishing protection against smallpox infection. This same level of immunity was found in 75 percent of those receiving a second dose and for up to 30 years for those receiving three doses. While the antibody level that protects against smallpox is unknown, research studies suggest that immunity lasts from 5 to 10 years and lengthens with additional boosters.[44, 45] Experts generally agree that smallpox vaccinations do not protect an individual for life. Since people born before 1972 received only one shot, it is safe to assume most no longer have any immunity. In essence, this means all U.S. citizens are dangerously susceptible to smallpox.

Unfortunately, should the U.S. desire to reintroduce preventive smallpox vaccinations (primary as well as revaccination), there are not enough doses yet to go around for 280 million Americans. When the eradication program ended, a number of countries along with the WHO stored enough vaccine for about 200 million people.[46] The WHO currently retains only 500,000 doses. The U.S. stockpile until very recently consisted of 15.4 million doses.[47]

Wyeth Laboratories produced the reserve stock of U.S. vaccine in the 1970s. While it is stored at -20° C to preserve its potency, time has taken its toll. Rubber stoppers on vials have begun to crumble and the vaccine's brilliant green dye has begun to lose its color. CDC officials purport that potency of the vaccine in the vials is nearly at full strength.[48] But Peter Jahling at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) in Frederick, Maryland, says, "50 percent of those doses are thought to be flawed."[49] These vials failed quality control tests because of elevated moisture levels, bringing into question the actual potency of the vaccine. To make matters worse, the stocks of *vaccinia* immune globulin, the antidote used to treat complications related to vaccination, has turned from clear to pink because the dye from rubber stoppers had leaked into the vials.

Since the anthrax attacks after September 11, 2001, steps have been taken to bolster U.S. defenses against smallpox. U.S. government stockpile consists of 15.4 million doses of smallpox vaccine. Research has shown that the vaccine can be safely diluted by at least five-fold, thereby providing 77 million doses. In response to this inadequate supply of vaccine, the U.S. government awarded a contract in November 2001 to two companies, Acambis PLC and Baxter Inc., to produce 209 million more doses of smallpox vaccine. Additionally, on March 29, 2002, Aventis Pasteur, a French drug company with operations in Swiftwater, PA, announced it had discovered 85 million doses of vaccine that had been in storage for years. The vaccine is apparently safe and is planned to be donated to the U.S. government.[50, 51, 52]

U.S. Response

In response to the concerns noted above, the Department of Defense (DOD) and National Institutes for Health (NIH) have recently stepped up

research efforts. Their goals are to develop a new vaccine and replace the current *vaccinia* immune globulin. In 1996, the DOD started funneling money toward the production of a stockpile of vaccine.[53] USAMRIID, in conjunction with the Salk Institute of Swiftwater, PA, had previously adapted the calf-lymph *vaccinia* vaccine to modern cell-culture production methods and has now conducted some safety and immunogenicity testing in human volunteers. In 1999, with the increased concern about terrorist use of smallpox and the dwindling supply of vaccine, the DOD and the HHS began parallel programs to produce more vaccine using the cell-culture process. However, mass production of an approved vaccine is not likely before 2004.[54]

In October 1999, NIH initiated an effort to improve civilian defense against bioterrorism. The goal was to address civilian needs not addressed by DOD. They requested research proposals in three areas. The areas to be researched are: (1) discovering and supplying drugs for mass treatment of and/or prevention of smallpox infection[55], (2) collecting and analyzing the genomes of pox viruses and then providing the information to others through a website[56], and (3) developing a new antidote against *vaccinia* complications[57]. The NIH should award the grants beginning September 2000. It is hoped this research will provide a defense for smallpox as well as insight as to what makes it so deadly.

Implications

Over the past decade, there has been increasing concern that rogue states and terrorists could use smallpox as a weapon. Its potential availability and natural lethality as well as our susceptibility and inadequate stockpiles of deteriorating vaccine make it potentially a very deadly weapon. The potential impact of the intentional release of smallpox is so great that in February 1999, USAMRIID personnel reported smallpox as one of "the two greatest [biological agents] with the greatest potential for mass casualties and civil disruption."[58] Because it could cause the most potential harm if used, CDC moved smallpox to the top of its bioterrorism threat list.[59]

A great fear is that the virus may exist outside the high-security storage laboratories in Atlanta and Siberia. Ken Alibek, a defector who was the former deputy director of the Soviet bioweapons program, reports Russia's smallpox weaponization program was active up until 1992 when President Yeltsin ordered it to end. With the collapse of the Soviet Union, scientists working in the program may have sold samples of the virus or hidden them for later sale to support themselves.[60] A recent unclassified intelligence report concludes that Iraq, North Korea, and Russia possess the deadly smallpox virus possibly for military use.[61]

The susceptibility of our population is equally worrisome. As of 1998, it has been estimated that 42 percent of Americans have never received a smallpox vaccination and less than 15 percent of the population is immune.[62] While the mortality of those in close contact to the virus could be 30 percent, the morbidity, or rate of incidence, would range from 60 to 90 percent.[63] Moreover, the vaccine we do have is old, limited, and perhaps less than fully effective. A release of smallpox would be cause for worldwide alarm. It is highly contagious and very stable in the environment. International airline travelers could unknowingly spread the virus around the world within days. Healthcare systems could be overwhelmed if an outbreak were not contained early. Most healthcare providers would not have immunity. Most negative pressure hospital rooms, would fill quickly. Citizens would probably insist on vaccination but current stocks will not meet the demand. Municipal plans for dealing with an outbreak are surely shallow, where they exist at all.[64]

Finally, *variola's* attributes make it the most feared biological terrorist or warfare weapon. Outbreaks in Europe in the 1970s illustrate its potential. In the 1970s German outbreaks, as many as 10 to 20 second generation cases, resulted from one case.[65] An outbreak occurred in Yugoslavia two years later, in spite of routine vaccination; the first case infected 11 other people and these 11 each infected an average of 13 more people.[66] One can only speculate on the extent of an outbreak today when so many people have not been vaccinated and those who have, have retained little immunity. In addition, the worldwide epidemic of HIV-AIDS has both increased the highly susceptible population, since smallpox was eradicated, and would now make mass vaccination almost impossible.

As grave as the situation may seem, there are sources who argue the likelihood of a targeted release of smallpox is relatively small. Terrorists may be able to obtain the virus with state sponsorship and release it covertly, but there has been little interest in biological terrorist weapons historically. W. Seth Carus's review of unclassified terrorist interests, both domestic and international, in biological warfare since the 1950s provided four conclusions:[67]

a. Only a few terrorists have attempted to acquire biological agents and fewer have attempted to use them.

b. The number of incidents involving use or attempted use of biological agents is extremely small, especially when compared to the thousands of known terrorists.

c. The number of known victims from unclassified terrorist attacks is limited to the 751 people who became sick during the 1984 Rashneeshee salad bar attacks. There were no known fatalities.[68] [Aum Shinrikyo, a Japan-based religious cult, produced biological agents and tried to use them…Fortunately, the Aum scientists apparently made mistakes in either the way they produced or disseminated the agents, and so far as is known, no one became ill or died as a result of the biological attacks.[69] The fatalities from Aum Shinrikyo's terrorist attacks on the Tokyo subway system resulted from the chemical agent sarin.]

d. To date, the relatively few terrorist groups that have attempted to use biological weapons have used crude dispensing technology, and with the exception of the late 2001 anthrax attacks in the U.S., have used poorly prepared or poor quality biological or chemical agents incapable of inflicting mass casualties. Aum Shinrikyo and the perpetrator(s) of the anthrax-through-the-mail attacks in the U.S. in late 2001 were the only groups known to have an interest in developing an aerosol capability and the Japanese cult's biological weapons program has been neutralized.

There are number of factors given to explain the infrequent use of biological agents by terrorists. They include:

a. Dependence on meteorological conditions makes agent delivery unpredictable.

b. Terrorists may fear for their own safety due to the potential for infecting themselves.
c. Terrorists may prefer a more precise weapon for their selected targets.
d. Terrorists may have moral qualms about using biological weapons.
e. Conventional weapons are easier to obtain and employ and may be considered adequate.
f. State sponsors may understand the implication of bioterrorism and promote restraint.
g. There is little precedence for the use of biological agents as terrorist weapons.
h. The technological constraints of obtaining, producing, and dispensing non-contagious agent are significant.[70]

Essentially, there are numerous hurdles to overcome to use smallpox as a weapon. Nevertheless, as long as the *variola* virus exists in any form—natural or engineered—the threat will be real. Whether the threat is small or large, it is prudent to require more study and research in all facets of a viable defense against the recurrence of smallpox.

Conclusion

Smallpox--has it been defeated and eradicated? Or, will it be used as a weapon of terror or war? Information derived from unclassified intelligence sources report that smallpox may indeed be in the hands of a few rogue states. The population of the United States, as well of the rest of the world, is all too susceptible to such a smallpox attack were it to occur. While the actual level of the threat can be debated, the consequences of the use of smallpox as a biological weapon would be overwhelming. Once released, smallpox is not only dangerous, it is currently practically unstoppable.[71] Our population, at the moment, is seriously vulnerable. Though unprepared, we are not unaware. We must act now and quickly. Our defenses must be strengthened against the possible future hostile use of smallpox by a terrorist group or an adversary government.

Steps in the right direction would include improving medical surveillance and other means of strengthening our public health infrastructure, development of a modern smallpox vaccine, and production of much larger quantities of vaccine than now exist in the stockpile of the present vaccine. Other important steps should include development of new antiviral drugs, improved diagnostics, and the expansion of education and a stronger tech base research program for medical defense. To do less than this would leave us dangerously vulnerable to future use of smallpox as an adversary weapon of terror or war.

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67. W. Seth Carus, "The Threat of Bioterrorism," *National Defense University Strategic Forum,* no. 127 (September 1997), n.p., online, Internet, 18 January 2000, available from http://www.ndu.edu/inss/strforum/forum127.html.

68. Statistics revalidated in W. Seth Carus, "Bioterrorism and Biocrimes: The Illicit Use of Biological Agents in the 20th Century," *Working Paper* (Washington, D.C.: National Defense University, December 1998) and Jonathan B. Tucker, "Historical Trends Related to Bioterrorism: An Empirical Analysis," *Emerging Infectious Diseases* 5, no. 5 (July-August 1999), 503.

69. W. Seth Carus, Threat of Bioterrorism, n.p.

70. Brad Roberts, ed., *Terrorism with Chemical and Biological Weapons: Calibrating the Risks and Responses* (Alexandria, VA: the Chemical and Biological Arms Control Institute, 1997), 66-70. Also, as Dr. David Franz noted in reviewing this manuscript, "Access and the moral constraints are probably the greatest deterrents to the use of smallpox as a terrorist weapon. Because of its highly-contagious nature, it would be unnecessary to weaponize it for use. It is likely that, even if the remaining isolates in Atlanta and Novosibrisk are ceremonially destroyed, illicit stocks or synthesis using the tools of molecular biology will make it available as a weapon in the future. The threat

cannot be calibrated; however, whether the threat is small or large, the potential impact of reintroduction of this virus to the human population is catastrophic. Prudence demands that we continue research which will help us control its spread and impact, should the unthinkable happen."

71. August Gribbin, n.p.